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REVIEW

Educational Paper: Aspects of clinical pharmacology in children—pharmacovigilance and safety

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Abstract Adverse drug reactions (ADRs) are a significant problem in children, affecting one in ten children in hospital. Within the community, one in 500 children will experience an adverse drug reaction each year. Pharmacovigilance has been useful in detecting suspected ADRs. However, most ADRs are unreported and often not suspected. Education of health professionals in relation to drug toxicity improves the reporting rate of suspected ADRs. Clinical trials are useful to evaluate the efficacy of drugs. They are, however, not the best way of looking at ADRs where surveillance following the widespread use of a drug is more appropriate. Alongside work by the regulatory agencies, independent investigators have helped collate data. This information has been useful in developing guidelines to prevent further cases of drug toxicity. Greater awareness and understanding of drug toxicity in children should result in more rational prescribing.

Keywords Children · Adverse drug reaction · Pharmacovigilance

Introduction

Drug toxicity unfortunately remains a significant problem in children. Drug toxicity can occur from medication errors and also from an adverse drug reaction (ADR). An ADR is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapeutic disease, or for the modification of physiological function" [19].

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Systematic reviews have demonstrated that approximately 10 % of children in hospital experience an ADR [13, 22]. The incidence of ADRs in children attending hospital outpatient clinics is much lower (1–1.5 %) [13, 22]. The incidence of ADRs in the community has been less extensively studied. ADRs are usually under-reported both in adults and in children. The true incidence of ADRs is unknown. We know from recent pharmacovigilance studies in Cuba that one in 500 children will experience an ADR each year [6].

Pharmacovigilance of medicines in adults is defined as the process of evaluating and improving the safety of marketed medicines. Many children, however, receive medicines that are either off-label or unlicensed. Paediatric pharmacovigilance has therefore been defined as the process of evaluating and improving the safety of medicines used in paediatric patients of all ages [10]. The aim of pharmacovigilance is to increase our understanding on drug toxicity in children. It is to be hoped that this improved understanding will result in greater patient safety as the aim should always be to reduce the incidence of ADRs. One needs to ensure that, as most ADRs are not reported, one reduces the actual incidence and not the reporting of ADRs.

Regulatory authorities and spontaneous reporting schemes

Regulatory authorities are responsible within individual countries for both the authorisation of medicines and also ensuring that there is a pharmacovigilance system in place. These consist of spontaneous reporting systems where it is recognised that under-reporting is a significant problem. Spontaneous reporting systems involve the reporting of suspected ADRs. They do not allow one to establish causality. They are, however, useful because they include the entire population and are therefore more likely to pick up

Table 1 Incidence of reported ADRs

Country	Years	ADR rate[a]	Reference
Sweden	1987–2001	226	24
Denmark	1998–2007	222	1
UK (Trent)	1998–2001	152	12
UK (East Anglia and Oxford)	1998–2001	52	12
Cuba (Camagüey)	2008	634	6
Spain	2004–2009	165 (2009)	3
Cuba (Camagüey)	2009	879	7
	2010	2031	7
UK	2000–2009	182	21

[a] Reports per million children per year

new previously unsuspected ADRs. There have been several studies which have described ADR reports received for children either on a national basis or on a regional basis [1, 3, 6, 7, 12, 21, 24]. These studies are summarised in Table 1 and are useful in relation to determining the incidence of ADRs in children. The benefits of educational interventions about pharmacovigilance have been shown to be successful in increasing the number of ADR reports submitted [6, 12, 25]. These studies have demonstrated that children experience a wide variety of ADRs similar to those described in adults.

Clinical trials

Clinical trials are essential in order to provide the scientific evidence base for the treatment of children with medicines. Safety within the clinical trials, however, is of key importance. ADRs and adverse events (AEs) in clinical trials are poorly reported [5, 14, 28]. Many studies previously did not even have an independent safety monitoring board which is considered essential for the safety of children [30]. These are now mandatory for clinical trials involving medicines in children in Europe. The reporting of ADRs and AEs in clinical trials sponsored by the pharmaceutical industry has been a long-standing area of concern [11, 15, 35, 37, 39]. The registration of clinical trials alongside the need to make data available is improving the situation, but it is important to recognise that investigators often report AEs and ADRs poorly in these situations and they are often overlooked. Clinical trials in children invariably involve children with illnesses. In contrast, clinical trials in adults may exclude the patients at greatest risk of drug toxicity;, for example, the elderly or those on polypharmacy. Clinical trials are of value in evaluating both the efficacy and effectiveness of medicines. They are, however, of less value in determining the safety of medicines. Clinical trials are usually powered for efficacy and not safety, as the latter requires a greater number of patients. Because clinical trials provide evidence regarding the efficacy of a new medicine, surveillance is essential following the widespread use of a medicine to detect less common ADRs. This surveillance is entirely dependent upon health professionals.

Case reports

New suspected ADRs are often reported as isolated case reports [23, 26]. These initial case reports are either rare, isolated events which are not considered to be a problem in the majority of patients in many cases. In other cases, however, they highlight a new significant toxicity as illustrated by the grey baby syndrome following the use of chloramphenicol [34], hepatotoxicity of sodium valproate [16], the propofol syndrome following the use of propofol as a sedative in critically ill children [29], visual field defects and vigabatrin [20] and precipitation of calcium and ceftriaxone in neonates [8]. Following on these case reports, subsequent studies have either performed additional scientific research [32, 36] or collected data either nationally or internationally [9, 17, 27, 38]. The subsequent studies have then been extremely useful in developing guidelines to help reduce the risk of subsequent drug toxicity (Table 2). In some cases, this is by the contraindication of the drug for certain indications. Examples of this include the removal of salicylates as an over-the-counter medicine for paediatric patients and the avoidance of the use of propofol as a sedative in critically ill children. In other cases, it is by more selective use of the drug in question. It is important to recognise that this information is dependent upon the initial publication of the suspected case reports. Another method of

Table 2 Time from publication of initial case reports to guidance on avoiding ADRs

Drug	ADR	Case report published	Guidance on avoiding ADR published
Chloramphenicol	grey baby syndrome	1959	1960
Sodium valproate	Hepatotoxicity	1979	1987
Propofol	Propofol infusion syndrome	1992	1998
Salicylates	Reye's syndrome	1965	1980
Ceftriaxone	Precipitation of calcium	2006	2008
Vigabatrin	Visual field defects	1997	1998

collating data is by performing a systematic review of the published literature. Systematic reviews of the safety of medicines are useful in identifying both the risk of toxicity and also side effects to health professionals [2, 4]. In certain cases following the publication of initial case reports of a possible ADR, there remains uncertainty as to whether there is a positive association between the drug and the ADR or not. An example of this includes the significance of QT prolongation with atomoxetine, a medication used for the treatment of ADHD. There have been several studies describing mild prolongation of the QT interval, but the clinical significance of this remains uncertain [33].

Reducing ADRs

The aim of pharmacovigilance is to reduce the incidence of ADRs by detecting risk factors for drug toxicity. In some cases, this is achieved by greater scientific understanding of the mechanisms of drug toxicity in paediatric patients. An example of this is the impaired drug metabolism in neonates which resulted in the grey baby syndrome following the use of chloramphenicol [34]. Recognition that neonates had impaired drug metabolism and required lower doses prevented further cases of the grey baby syndrome. Kernicterus associated with the use of sulphonamides in neonates was due to its protein-displacing effect on bilirubin [18, 31]. Sulphonamides and other highly protein-bound drugs such as ceftriaxone are therefore not recommended in sick neonates.

Summary

Pharmacovigilance and rational prescribing of medicines need to be more closely intertwined as increasing knowledge about drug toxicity should result in more rational prescribing. Unfortunately, this is often not the case, and paediatric patients still receive medicines that are contraindicated, for example, propofol as a sedative in critically ill children. Paediatricians can play a key role by, firstly, always considering the possibility that a child's symptoms may be explained by an ADR. Additionally, we need to be aware of the risks of drug toxicity and consider the risk/benefit ratio before prescribing any medicines.

Conflict of interest None.

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